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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/044,696	03/18/98	BARCHFELD G	1393.002

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EXAMINER	
DEVI, S	
ART UNIT	**PAPER NUMBER**
1645	19

DATE MAILED: 01/12/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/044,696	Barchfeld et al.
Examiner	**Group Art Unit**
S. Devi, Ph.D.	1645

☒ Responsive to communication(s) filed on *10/27/2000.*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-19, 21, and 23-30* is/are pending in the application.

Of the above, claim(s) *1-18* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *19, 21, 23, and 25-30* is/are rejected.

☒ Claim(s) *24* is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *16.*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Applicants' Amendment

1) Acknowledgment is made of Applicants' amendment filed 10/27/00 (paper no. 17) in response to the non-final action mailed 04/25/00 (paper no. 15), which amendment has been entered.

Status of Claims

2) Claim 22 has been canceled via the amendment filed 10/27/00.

Claims 19 and 27 have been amended via the amendment filed 10/27/00.

Claims 1-19, 21 and 23-30 are pending in this application.

Claim 19, 21 and 23-30 are under examination.

The Giudice Declaration

3) Acknowledgment is made of Applicants' submission of the Giudice Declaration filed 10/27/00 (paper no. 18) under 37 C.F.R § 1.132. The contents of the Declaration are now moot in light of Applicants' amendments to the base claim and/or the new art applied in this Office Action and/or the withdrawal of previous rejections of record.

Information Disclosure Statements

4) Acknowledgment is made of Applicants' Information Disclosure Statement filed 07/20/00 (paper no. 16). The information referred to therein has been considered and a signed copy is attached to this Office Action (paper no. 19).

On page 3 of the amendment filed 10/27/2000, Applicants claim that they have not received an initialed copy of IDS submitted on 07 May 1998, 11 September 1998 and 18 July 2000. The record shows that an initialed copy of the IDS filed in May and September 1998 (paper no. 4 and 5) were provided to Applicants as attachments to the Office Action mailed 08/04/99 (paper no. 10). The IDS of July 2000 was filed after the previous Office Action was mailed out and therefore was not considered until now.

As per Applicants' request, a copy of the initialed IDS filed in May and September 1998 are resupplied to Applicants as attachments to this Office Action (paper no. 19).

Objection Maintained

5) The objection to the drawings made under 37 C.F.R 1.84 in paragraph 7 of the Office Action mailed 08/04/99 (paper no. 10) and maintained in paragraph 4 of the Office Action mailed 04/25/00 (paper no. 15) is still maintained for reasons set forth therein.

Rejection(s) Moot

6) The rejection of claim 22 made in paragraph 9 of the Office Action mailed 08/04/99 (paper no. 10) and maintained in paragraph 17 of the Office Action mailed 04/25/00 (paper no. 15) under 35 U.S.C. 112, first paragraph, as being non-enabled, is moot in light of Applicants' cancellation of the claim.

7) The rejection of claim 22 made in paragraph 16 of the Office Action mailed 08/04/99 (paper no. 10) and maintained in paragraph 19 of the Office Action mailed 08/04/99 (paper no. 10) under 35 U.S.C § 102(a) as being anticipated by Pizza *et al.* (WO 97/02348, published 23 January 1997 - Applicants' IDS) (Pizza *et al.*, WO '348) is moot in light of Applicants' cancellation of the claim.

Rejection(s) Withdrawn

8) The rejection of claims 19, 21 and 24-30 made in paragraph 17 of the Office Action mailed 04/25/00 (paper no. 15) under 35 U.S.C. 112, first paragraph, as being non-enabled, is withdrawn.

9) The rejection of claim 27 made in paragraph 10(c) of the Office Action mailed 08/04/99 (paper no. 10) and maintained in paragraph 17 of the Office Action mailed 04/25/00 (paper no. 15) under 35 U.S.C. 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

10) The rejection of claims 19, 21 and 24-30 made in paragraph 20 of the Office Action mailed 04/25/00 (paper no. 15) under 35 U.S.C. 112, first paragraph, as being non-enabled, is withdrawn.

11) The rejection of claims 19, 25, 26 and 30 made in paragraph 21 of the Office Action mailed 04/25/00 (paper no. 15) under 35 U.S.C. 112, first paragraph, as being non-enabled with regard to the scope, is withdrawn.

12) The rejection of claim 27 made in paragraph 10(c) of the Office Action mailed 08/04/99

(paper no. 10) and maintained in paragraph 18 of the Office Action mailed 04/25/00 (paper no. 15) under 35 U.S.C. 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendments to the base claim.

13) The rejection of claims 19, 21, 23 and 25-30 made in paragraph 16 of the Office Action mailed 08/04/99 (paper no. 10) and maintained in paragraph 19 of the Office Action mailed 08/04/99 (paper no. 10) under 35 U.S.C § 102(a) as being anticipated by Pizza *et al.* (WO 97/02348, published 23 January 1997 - Applicants' IDS) (Pizza *et al.*, WO '348), is withdrawn.

New Rejection(s)

Applicants are asked to note the new rejections made in this Office Action. The reference of Domenighini *et al.* (US 6,149,919) was not or could not be applied previously since it got issued well after the mailing of the previous Office Action on 04/25/2000.

Rejection(s) under 35 U.S.C. § 102

13) The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) The invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

14) Claims 19, 21, 23 and 25-27 are rejected under 35 U.S.C. § 102(e) as being anticipated by Domenighini *et al.* (US 6,149,919 with an effective filing date of 12/30/1992) ('919) as evidenced by Tommaso *et al.* (*Infect. Immun.* 64: 974-979, 27 February 1996, already of record) or Partidos *et al.* (*Immunology* 89: 483-487, December 1996, already of record).

The base claim 19 is drawn to a method of immunizing a vertebrate subject comprising parenteral administration of an adjuvant selected from the group consisting of LT-R72 and LT-K63 in combination with a pharmaceutically acceptable vehicle and at least one selected antigen. The limitation "adjuvant" in the claim is viewed as inclusive of both a mucosal and a non-mucosal adjuvant.

Domenighini *et al.* ('919) disclose a method of vaccinating, i.e., immunizing, an individual (i.e., a vertebrate subject) comprising parenterally administering an immunologically effective

amount of a detoxified mutant of *E. coli* heat-labile enterotoxin comprising serine to lysine amino acid replacement (i.e., substitution) at position 63 in the subunit A of the enterotoxin (i.e., LT-K63) (see claims 4 and 1, and column 8, lines 38-57). The mutant enterotoxin further comprises a pharmaceutically acceptable carrier or a vehicle (see column 7, third full paragraph) and bacterial cell wall components, i.e., selected antigens (see column 7, last paragraph). The mutant LT-comprising composition is conventionally administered "parenterally, i.e., by injection either subcutaneously or intramuscularly", or used for "transdermal", i.e., transcutaneous, application (see column 8, lines 55-60). The pharmaceutically acceptable carrier may be glycerol, ethanol, saline, water or oil droplets (see column 8, lines 25-27 and column 7, lines 48-52), all of which qualify as topical vehicles.

That the prior art mutant LT comprising serine to lysine amino acid replacement at position 63 is an art-recognized adjuvant was well known in the art before the effective filing date of the instant invention. For instance, Tommaso *et al.* teach the LTK63 detoxified mutant of ADP-ribosylating heat-labile enterotoxin of *E. coli* as an effective adjuvant when administered along with a carrier and a selected antigen (see abstract and page 975, left column). Similarly, Partidos *et al.* teach a detoxified mutant of ADP-ribosylating *E. coli* heat-labile toxin, LT-K63, as an adjuvant in a method of immunizing mice by administering the mutant in combination with phosphate-buffered saline and a selected antigen, such as, a measles viral antigen (see abstract; page 484, left column, and page 485, right column).

The teachings of Domenighini *et al.* ('919) anticipate the instant claims. Tommaso *et al.* or Partidos *et al.* is **not** used as a secondary reference in combination with Domenighini *et al.* ('919), but rather is used to show that every element of the claimed subject matter is disclosed by Domenighini *et al.* ('919), because Tommaso *et al.* or Partidos *et al.* teach that LTK63 detoxified mutant of heat-labile enterotoxin of *E. coli* serves as an an effective adjuvant to a selected antigen. See *In re Samour* 197 USPQ 1 (CCPA 1978).

Claims 19, 21, 23 and 25-27 are anticipated by Domenighini *et al.* ('919).

Rejection(s) under 35 U.S.C. § 103

15) Claims 28-30 are rejected under 35 U.S.C. §103(a) as being unpatentable over Domenighini *et al.* (US 6,149,919) as applied to claim 19 above, and further in view of

Rappuoli *et al.* (WO 95/17211, published 06/29/95 -Applicants' IDS) (WO '211).

The teachings of Domenighini *et al.* ('919) are described above which do not expressly teach the claimed method wherein the antigen is administered prior to or subsequent to the administration of the antigen, or concurrently with the administration of the antigen.

However, such methods of administration of a mutant heat-labile LT toxin of *E. coli* and a selected antigen are known in the art. For instance, Rappuoli *et al.* (WO '211) teach a method of immunization wherein a mutant heat-labile LT toxin of *E. coli* adjuvant and a selected antigen are administered simultaneously (i.e., concurrently) or sequentially or separately (see claims 13 and 14 of Rappuoli *et al.*).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to administer Domenighini's composition containing the detoxified mutant of *E. coli* heat-labile enterotoxin, LT-K63, and the selected antigen to a vertebrate host using Rappuoli's method of separate or sequential or concurrent administration to produce the method of the instant invention, with a reasonable expectation of success. Given that such methods of administration are conventionally practiced in the art, one skilled in the art would have been motivated to use such methods for the expected benefit of inducing a desired type of immune response, for the expected benefit of inducing a selected type of immune response.

Claims 28-30 are *prima facie* obvious over the prior art of record.

Prior Art

16) The prior art made of record and not relied upon currently in any of the rejections is considered pertinent to Applicants' disclosure:

- Detoxified or non-toxic mutants of bacterial ADP-ribosylating toxins have been successfully used in the art as parenteral adjuvants along with a selected antigen. For example, Gajewzyk *et al.* (WO 95/34323, published 21 December 1995 - Applicants' IDS) teach a method of immunizing mice or a human (i.e. the vertebrate subject) by administering a non-toxic adjuvant comprising a detoxified mutant of a *Bordetella pertussis* ADP-ribosylating toxin, K9G129 PT analogue, and at least one selected antigen, such as, ovalbumin or a non-*Bordetella* antigen (see page 32, lines 14-16; page 11, lines 3-10, and claims 25, 28 and 29). The K9G129 PT analogue has two amino acids replaced (see page 10, lines 7-12). The two components are co-administered

to the host in immunologically effective amounts (see claim 25). The term "coadministration" means simultaneous administration or administration within a few days (see page 11, lines 20-23). The composition may contain a physiologically acceptable carrier such as water, saline, glycerol or ethanol (see page 17, lines 8-11) and may be administered subcutaneously or intramuscularly (see page 17, lines 15-22). The genetically detoxified pertussis holotoxin has at least one amino acid removed (i.e. deletion) or replaced (i.e. substitution) in the holotoxin (see claim 12). The K9G129 adjuvant is evaluated with human pediatric combination vaccines, for example, a DTP vaccine (see page 15, lines 23-26 and page 13, lines 15-17).

- Granoff *et al.* (US 6,030,619) disclose the use of LT-R72 and LT-K63 mutant toxins as adjuvants along with vaccine compositions (see column 20). Granoff *et al.* further teach that such compositions are administered parenterally, i.e., subcutaneously or intramuscularly (see column 21, lines 37-39).

- Fasano *et al.* (US 5,908,825) disclose the intranasal administration of LT-R72 or LT-K63 adjuvant along with antigens such as ova. Although LT-R72 has been found to be more immunogenic than LT-K63 mutant, it has been found to be reactogenic in animal models (see columns 11 and 12).

- Ghihara (US 5,985,243) discloses the use of LT K63 as an adjuvant along with a bacterial antigen (see column 10, lines 1-15).

- Glenn *et al.* (US 5,980,898) disclose the transcutaneous, i.e., parenteral, immunization with potent adjuvants such as *E. coli* heat-labile enterotoxin (LT) and cholera toxin (CT). See column 10, third full paragraph.

- Clements *et al.* (WO 9606627 - Applicants' IDS) disclose parenteral administration to mammals of an adjuvant mutant LT (mLT) along with an antigen (see page 20, lines 15-18).

Objection(s)

17) Claim 24 is objected for being dependent from a rejected base claim.

Remarks

18) Claims 19, 21 and 23-30 stand rejected. Claim 24 is free of prior art currently of record. However, the claim stands objected to, but would be allowable if rewritten in an independent form

including all of the limitations of the base claim and any intervening claims.

19) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1 (CM1). The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center's telephone number is (703) 308-4242, which is able to receive transmissions 24 hours a day and 7 days a week.

20) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

SD
S. Devi, Ph.D.
Patent Examiner
January 2001